REMARKS

I. Claim Amendments

Claims 1-20, 22-33 and 68 are pending in the present application. Applicant amended claim 1, to recite that the claimed device includes just one calibration zone.

II. Claim rejections 35 USC 112

Claim 6 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because, allegedly, it is not clear how the fourth zone and the fifth zones are overlapping if a calibration zone is placed between these two zones. Office Action, page 2.

Applicants respectfully submit that claim 6 does not require the calibration zone to be placed between the fourth and fifth zones. Thus, Applicants would appreciate clarification of the basis for this rejection.

III. Rejections Under 35 USC Section §103

A. Claims 1-3, 5, 9-13, 20, 22-25, 28, 30-33 and 68 are not Obvious over were Good et al., in view of Wei et al. or Robinson et al.

Claims 1-3, 5, 9-13, 20, 22-25, 28, 30-33 and 68 were rejected under 35 U.S.C. § 103(a) in view of Good et al. (US Patent 6,194,240) (which may also be referred to herein as "Good"), in combination with Wei et al. (US 2003/0119203) (which may also be referred to herein as "Wei") or Robinson et al. (US 5,726,064) (which may also be referred to herein as "Robinson"). In summary, the rejection was premised on the assertion that Good et al. disclose a device of several different specifically described zones, which have various compositions, with some of the zones overlapping with each other. It was stated that Good et al. differ from Applicants' invention in failing to teach a calibration zone comprising an immobilized binding agent having an affinity for the labelled non-immobilized molecule. Office Action, page 4. Wei et al. and Robinson et al. were relied upon to compensate for this deficiency. Applicants respectfully traverse this rejection for the reasons discussed below.

Applicants submit that a person of ordinary skill in the field of endeavour of Applicants' claimed invention would find no reason, motivation or suggestion in the aforementioned references to combine the teachings of Good et al. with Wei et al. and/or Robinson et al. to achieve the Applicants' claimed device.

Good et al. disclose a device comprising a porous material having a receiving zone, a reagent zone containing antibodies labelled with colloid gold particles and a test zone containing immobilised molecules of the specified analyte. Downstream from the test zone, the device described by Good et al. comprises a calibration zone which indicates the presence of a sample. As apparent from column 6, lines 53-67, Good et al. disclose a positive/negative test and do not determine the amount of a certain analyte. In the above paragraph it is stated that "*...a positive sample will inhibit the formation of a visible line in the test zone...*" and that "*Normally a negative oral fluids sample will produce two colored lines, one in the test zone region and one in the control zone region and a positive oral fluids sample will show only one line in the control zone region.*". Good et al. do not disclose a device for the quantitative determination of an analyte in a sample wherein the content of the analyte present in the sample, is calculated from a signal obtained in the test zone and a signal obtained in the calibration zone.

Wei et al. disclose a lateral flow device for determining an analyte in a sample using the "sandwich" assaying technique. The lateral flow device according to Wei et al. comprises a test zone having an immobilised capture reagent, such as an antibody, specifically binding to the analyte, to be determined. The device described by Wei et al. comprises a calibration zone, which comprises two or more (e.g. three, four or more) control lines. (see Figures 1, 1A and 1B, paragraphs [0012] and [0039], and claim 1 section (b)(ii) stating that the "*...calibration zone comprising at least first and second control lines,.....*".) The amount of analyte may be determined by comparing the intensity level of a detection line 24 generated at the detection zone 31 with the intensity level of the calibration lines to calculate the amount of the analyte present. *See*, e.g., paragraph [0039]. Example 3 indicates that the intensities in the three calibrations lines are 0.54 ng, 5.4 ng and 54 ng analyte, respectively. The concentration of analyte of an unknown sample could then be visually determined by comparing the intensity level of the detection line with the intensity level of the three calibration lines.

Thus, Wei et al. disclose an assay device for the semi-quantitative determination of an analyte in a sample which provides an approximate value of the analyte, based on comparison of a detection line intensity level to with the intensity level of two or more calibration lines.

Robinson et al. describe a device for determining a ligand in a sample, similar to that of Wei et al. in that Robinson et al.'s device preferably includes more than one calibration surface. In column 3, lines 55-58, it is stated that, for a quantitative method, the number of calibration surfaces is preferably greater than one and more preferably greater than or equal to four. In Robinson et al. the calibration surface utilizes a movable second specific binding reagent which binds on the calibration surface (e.g. see claims 2, 6 and 7). Thus, Robinson et al. disclose the use of two movable specifically binding molecules, one for the binding in the measurement zone and one for binding in the calibration zone. The device described by Robinson et al. uses a different technique than Applicants' claimed invention. For example, the calibration zone defined in Applicants' claimed invention uses one mobile specific binding reagent, and Applicants' claimed device has a construction distinct from that of Robinson et al.

In contrast, Applicants' claimed invention relates to an analytical device for the quantitative determination of an analyte in a sample. Applicants' device comprises a first zone (which also may be referred to herein as "an application zone"), onto which an analyte sample can be applied, and a second zone (which may be referred to herein as a "conjugate zone") comprising a non-immobilized molecule (e.g., an antibody) capable of binding specifically to the analyte of interest present in the sample. The conjugate zone also includes a detectable label.

Downstream from the conjugate zone is a fourth zone (also referred to herein as a "test zone"), comprising a molecule of the same type as the one to be assayed or an analogue thereof in an immobilized state. A calibration zone is located downstream from the test zone. The calibration zone comprises an immobilized binding agent (e.g., an antibody) having an affinity for the labelled non-immobilized molecule capable of binding specifically to the analyte to be assayed. The amount of the analyte present in the sample is determined from a signal obtained in the fourth zone and a signal obtained in the calibration zone.

The construction and function of the Applicants' device is significantly and fundamentally different from that of Good et al., at least because Good et al.'s device lacks the calibration zone

and because it does not measure the amount of the analyte, but measures only the presence or absence of the analyte. Thus, Good et al.'s device is a positive/negative test device. The devices of Wei et al. and Robinson et al. are also significantly distinct and different from Applicants' claimed device for the reasons set forth above. In summary, Wei et al. relate to a device performing a semi-quantitative test (wherein the intensity level of the test line is compared to the more than one calibration lines) and the device described by Robinson et al. relates to a semi-quantitative or a quantitative test using two different movable specifically binding molecules, one for the binding in the measurement zone and one for binding in the calibration zone. In contrast, Applicants' claimed device is directed to a quantitative test giving the content of the analyte of interest using only one movable specifically binding molecule for the binding in the measurement zone and in the calibration zone.

The problem solved by the present invention is to provide a device which makes it possible to monitor small day-to-day changes in the level of an analyte of interest on a daily basis or during selected time intervals in a cheap, highly sensitive, reproducible, and precise manner, which requires a minimum of handling steps and which is easy to perform.

None of the cited prior art documents solves or touches upon the problem solved by the Applicants' invention. Furthermore, the information provided in the cited documents cannot be used by a skilled person to solve to problem solved by the present invention.

None of the references relied upon suggest a specific need for a design, nor a specific focus in the market, on lateral flow devices which solve the problem solved by the claimed invention. Furthermore, there is a significant number of combinations of designs, detection techniques, construction techniques and algorithms available in the combination of the three references from which a person of ordinary skill in the art would have to selectively pick a particular combination of features (with no guidance in the references to do so) in an effort to obtain Applicants' claimed device.

Therefore, a person skilled in the art would have no reason, based on the cited references to arrive at the combination of features to provide the quantitative test device defined in the Applicants' claims, which solves the problem of the present invention.

Accordingly, claim 1 is not obvious under 35 U.S.C. §103.

B. Claims 4, 6, 7, 8, 14-16, 17, 18-19, 26, 27 and 29 are not obvious over Good et al., Wei et al., Robinson et al., in view of Polzius et al., Schlipfenbacher et al., Davis et al., Lee et al., Henderson et al., Robinson et al., Frushour et al. or Sundrehaqen.

Claims 4 and 6 were rejected as obvious over Good et al. in view of Polzius et al. (U.S. Patent 6,130,097) (also referred to herein as "Polzius ") or Schlipfenbacher et al. (U.S. Patent 5,160,486) (also referred to herein as "Schlipfenbacher"). It was alleged that Polzius teaches that it is known in the art to overlap zones on a test strip to provide for fluid contact of the zones. Schlipfenbacher was cited for its alleged teaching that overlapping zones on a test strip are known in the art. It was concluded that it would have been obvious to combine Good et al. With Polzius et al. and Schlipfenbacher et al. to obtain the device of claims 4 and 6, with overlapping zones.

The remaining claims, rejected as obvious, were similarly rejected by combining Good et al. with other references as follows:

- Claims 7 and 8: over Good et al., Wei et al., or Robinson et al. in view of Davis et al. (U.S. Patent 6,352,862) (also referred to herein as "Davis") because allegedly Davis et al.'s teaching of several labeled specific binding reagents and multiple reagents, combined with Good et al. would have made claims 7 and 8 obvious.

- Claims 14-16: over Good et al., Wei et al., or Robinson et al. in view of Lee et al. (WO 02/04671) (also referred to herein as "Lee") because allegedly Lee's disclosure of bovine serum albumin (BSA), combined with Good et al. would have made obvious incorporating spacer molecules, including BSA, into Good et al.'s device, thereby rendering claims 14-16 obvious.

- Claim 17: over Good et al. and Wei et al. in view of Lee et al., and Henderson et al. (U.S. 2004/0072248) (also referred to herein as "Henderson") based on Henderson's alleged teaching of CMO conjugated to bovine serum albumin and to an estrogen, and used as a binding substance, immobilized on the surface of a test strip and used in assays. It was reasoned that it would have been obvious to incorporate CMO into Good's modified

device to render prima facie obvious claims 14-16.

- Claims 18 and 19: Over Good et al. and Wei et al. or Robinson et al. in view of Frushour et al. (US 2003/0059951) (also referred to herein as "Frushour ") because Frushour's alleged teaching of the spatial separation zones on a test strip and the flow rate characteristics of the porous solid phase material can be selected to allow adequate reaction times in which the necessary specific binding can occur, and allow the labeled antibody in the labeled antibody zone to dissolve through the porous solid phase material.

It was asserted that a person of ordinary skill in the art would have found it obvious to combine teachings of the references, to achieve the device of Good et al. with a changed length of the third zone.

- Claims 21-23: over Good et al. in view of Robinson et al. (WO 95/1 6914) ("Robinson"), based on Robinson's alleged teaching of the calibration zones, in which a calibration reagent is immobilized and has biospecific affinity for the analyte or the binding partner of interest. Thus, according to the Office Action, it would have been obvious to one of ordinary skill in the art to include the use of a calibrator zone into the device of Good.

- Claims 26, 27 and 29: over Good et al. and Wei et al. and Robinson et al. in view of Sundrehagen (U.S. 6,716,641) (also referred to herein as "Sundrehagen") based on Sundrehagen's alleged teaching of using reagents in zones of a test strip. According to the Office Action, Sundrehagen discloses that the use of the reagents prevents non-specific binding of the detector reagent and/or analyte.

Applicants do not concede that characterization of the references in the Office Action is correct. Even if, arguendo, it were correct, Applicants submit that, these rejections are misplaced as a matter of law.

One test for a proper obviousness rejection requires the finding of some teaching, suggestion or motivation provided by the prior art, to combine the teachings of the prior art. The Office Action failed to establish such teaching, suggestion or motivation in the prior art.

> Furthermore, none of Good et al., Wei et al., Robinson et al., Polzius et al., Schlipfenbacher et al., Davis et al., Lee et al., Henderson et al., Freshour et al. or Sundrehagen ("secondary references") discloses or suggests the calibration zone as now recited in claim 1 (and thus in all the dependent claims included in the obviousness rejection). For at least this reason, the combination of Good et al. with the secondary references (even if arguendo such a combination were proper), would not have suggested to a person of ordinary skill in the art the invention defined in claims 4, 6-8, 14-19, 21-23, 26, 27 and 29.

While the Supreme Court in *KSR International Co. v. Teleflex Inc.,* 2007 WL 1237837 (U.S.) 82 USPQ 2d 1385 rejected the use of the teaching/suggestion/motivation (TSM) test as the only test for obviousness analysis, it did not eliminate it as a possible test. The Court recognized that a showing of teaching, suggestion or motivation to combine the prior art elements to meet the claimed subject matter could provide a helpful insight in the determination of whether the claim(s) under consideration are obvious. Furthermore, the Court held that the obviousness analysis needs to be explicit and cannot be sustained by mere conclusory statements. According to the Court, a patent claim directed to several elements is not obvious based on a mere showing that each of the elements is known in prior art, and that a reason needs to be identified for prompting a person of ordinary skill to combine the prior art elements in the same way that the claimed invention does.

All obviousness rejections in the Office Action are based on selectively picking isolated elements of several prior art disclosures and combining them into a mosaic resembling Applicants' invention. There is no showing of a rational underpinning as to why a person of ordinary skill, aware only of the prior art (but not Applicants' claimed invention), would have known to:

1) choose such specific elements; and
2) combine them in the precise manner needed to obtain Applicants' claimed invention.

For all these reasons Applicants' respectfully request withdrawal of all obviousness rejections.

IV. Request for Allowance

Applicants respectfully submit that all claims are in condition for allowance, an indication of which is solicited.

In the event that any outstanding issues remain, Applicants respectfully request the courtesy of a telephone call to the undersigned counsel to resolve such issues in an expeditious manner and place the application in condition for allowance.

In the event that any variance exists between the fees enclosed herewith and those deemed necessary by the US Patent and Trademark Office to enter and consider this amendment and response, or to maintain the present application pending, please credit or charge such variance to the undersigned Deposit Account Number 50-2478.

Respectfully submitted,

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